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Minimally-invasive estimation of patient-specific end-systolic elastance using a biomechanical heart model

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Abstract. The end-systolic elastance (E_{es}) – the slope of the end-systolic pressure-volume relationship (ESPVR) at the end of ejection phase – has become a reliable indicator of myocardial functional state. The estimation of E_{es} by the original multiple-beat method is invasive, which limits its routine usage. By contrast, non-invasive single-beat estimation methods, based on the assumption of the linearity of ESPVR and the uniqueness of the normalised time-varying elastance curve $E^N(t)$ across subjects and physiology states, have been applied in a number of clinical studies. It is however known that these two assumptions have a limited validity, as ESPVR can be approximated by a linear function only locally, and $E^N(t)$ obtained from a multi-subject experiment includes a confidence interval around the mean function. Using datasets of 3 patients undergoing general anaesthesia (each containing aortic flow and pressure measurements at baseline and after introducing a vasopressor noradrenaline), we first study the sensitivity of two single-beat methods – by Sensaki et al. and by Chen et al. – to the uncertainty of $E^N(t)$. Then, we propose a minimally-invasive method based on a patient-specific biophysical modelling to estimate the whole time-varying elastance curve $E^{\text{model}}(t)$. We compare E_{es}^{model} with the two single-beat estimation methods, and the normalised varying elastance curve $E^{N,\text{model}}(t)$ with $E^N(t)$ from published physiological experiments.

Keywords: Time-varying elastance · End-systolic elastance estimation · Patient-specific biophysical modelling

1 Introduction

The relation between ventricular pressure (P) and volume (V) at the end of ejection is described by the preload and afterload independent end-systolic pressure-volume relationship (ESPVR). The slope of ESPVR – the so-called end-systolic elastance, E_{es} – and its volume intercept (V_0) allow to derive the time-varying

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elastance $E(t) = P(t)/(V(t) - V_0)$, see Fig. 1. Under physiological loading ranges, the E_{es} is known to be closely related to the active properties of the myocardium [1, 13], and is assumed to be itself preload and afterload independent, and so the ESPVR to be linear. Even though the load dependency of E_{es} has been experimentally shown [1], the linear approximation of ESPVR and the subsequent analysis of its derived indicators have been proven to be clinically useful for performance assessment and monitoring of failing hearts, and for studying the interaction between the heart and vasculature (e.g. by assessing the so-called ventricular-arterial coupling, $V_{va} = E_{es}/E_a$, with E_a being the arterial elastance [13]).

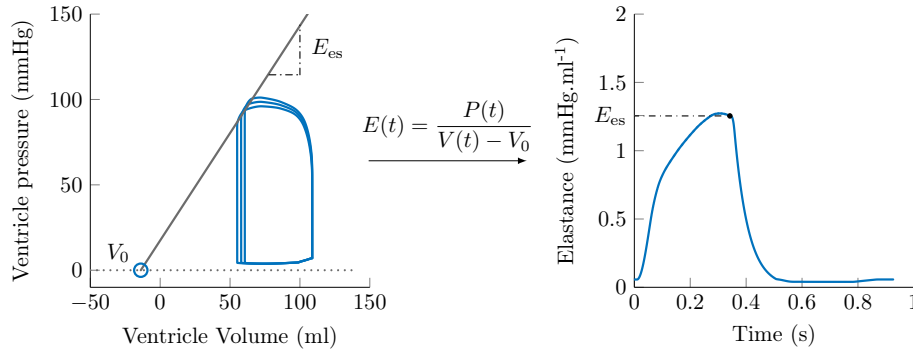


Fig. 1. Example of the model-based determination of E_{es} , V_0 and $E(t)$

Originally, E_{es} and ESPVR were obtained using a multiple-beat measurement technique. A linear regression was fitted on the end-systolic P-V points measured at different loading conditions (e.g. by inferior vena cava occlusion, or administration of vasopressors), during cardiac catheterisation. The associated technical issues led to a development of single-beat methods [14, 15], which allow to estimate E_{es} and ESPVR non-invasively [5, 7]. We hypothesised that the estimation of E_{es} using such methods is, however, too sensitive to their parameters to obtain a reliable patient-specific result.

By calibrating a biomechanical model of heart and vasculature [2, 4] using aortic pressure and flow data, we can simulate the entire P-V loop and reproduce minimally-invasively the original multiple-beat measurement method. We aimed at comparing the E_{es} obtained by the single-beat methods or obtained by a method based on patient-specific biophysical modelling. Furthermore, we evaluated the properties of the derived time-varying elastance after spatial-temporal normalisation [16].

2 Methods

2.1 Data and models

Patients and procedures Three patients undergoing general anaesthesia (GA) for neuroradiological intervention, for whom a continuous arterial pressure and cardiac output monitoring were indicated, were included in the presented observational study, approved by the ethical committee of the Société de Réanimation de Langue Française (CE-SRLF 14-356). The data collection is described in detail in [10]. Briefly, after GA induction, a transthoracic echocardiography (TTE) was performed to obtain cardiac geometry information. A transoesophageal Doppler probe (Deltex Medical, Chichester, UK) was inserted into the oesophagus in order to continuously measure the aortic flow. During the procedure, the anaesthetist could need to raise blood pressure using intravenous administration of $5\mu\text{g}$ of noradrenaline (NOR). The neuroradiologist cannulated aorta through femoral puncture, and inserted a guidewire. A fluid-filled mechanotransducer was connected to obtain the aortic pressure waveform.

Biomechanical model of heart and vasculature The model used in this study was a combination of a biomechanical heart and Windkessel circulation models connected together to represent the cardiovascular system. The heart model was derived from a previously validated complete three-dimensional (3D) model [4] by model reduction [2]. While the entire geometry was reduced to a sphere, all the passive and active properties were kept as in the 3D model. The passive part of myocardium was modelled according to Holzapfel and Ogden [8], and adjusted using experimental data [11]. The active contraction was based on Huxley's sliding filament theory [9]. The circulation was represented by a 2-stage Windkessel model connected in series (proximal and distal capacitances and resistances). In turning the model into patient-specific regime, see also [3, 12], first the Windkessel model parameters were calibrated by imposing the measured aortic flow and tuning the resistance and capacitance parameters, in order to fit the simulated and measured aortic pressure. Then, geometry and passive myocardial properties were calibrated using TTE data. The timing of the electrical activation was adjusted using ECG timings (in particular, the action potential duration in line with the ST interval). Finally, the myocardial contractility was tuned to minimise the difference between the simulated and measured aortic flow and pressure. The model calibration as described above was performed in two different conditions – at baseline and at maximal effect of NOR – to explore comparatively the cardiovascular effect of NOR. Data processing and signal analysis were performed in Matlab, (Natick, Massachusetts, USA) in which the model [2] was implemented into a library named CardiacLab.

2.2 Single-beat estimation of E_{es}

Method by Senzaki et al. [14] The method is based on the characteristics of the time-varying elastance $E(t)$ described in detail by Suga et al. [16]. In

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brief, the normalised $E(t)$ – with respect to the time at end-systole (t_{\max}) and maximal elastance value (E_{es}), i.e. $E^N(t) = \frac{E(t/t_{\max})}{E_{\text{es}}}$ – was found to be consistent across subjects and across varying loading conditions [16]. This principle therefore allows to identify a particular time-point on the subject and physiology independent “universal” $E^N(t)$, if the ratio $\frac{t}{t_{\max}}$ is known.

To estimate E_{es} , the following values need to be obtained: 1) the end of isovolumic contraction (t_d) assessed by TTE; 2) ventricular pressure at the opening of aortic valve (measured by aortic catheter); 3) ejection time (from end-diastole to end-systole) by TTE; and 4) ventricular volumes (end-diastole and end-systole), accessed by TTE. We can then apply the formula by Senzaki et al. [14]:

$$E_{\text{es}}^{\text{senzaki}} = \left(\frac{P_{\text{ed}}}{E_d^N} - P_{\text{es}} \right) / \text{SV}, \quad (1)$$

where $E_d^N = E^N(t_d)$, P_{ed} being the aortic end-diastolic pressure, P_{es} the aortic end-systolic pressure, SV the stroke volume.

Method by Chen et al. [5] This method is derived from the original method of Senzaki by optimising the following linear regression to estimate E_d^N :

$$E_d^{N,\text{modified}} = 0.0275 - 0.165 \cdot \text{EF} + 0.3656 \cdot \frac{P_{\text{ed}}}{P_{\text{es}}} + 0.515 \cdot E_d^N, \quad (2)$$

EF being the ejection fraction measured by TTE as the ratio between SV and the end-diastolic volume. Finally, $E_d^{N,\text{modified}}$ is used in Eq. (1) to estimate $E_{\text{es}}^{\text{chen}}$. We used the methods of Senzaki and Chen to predict E_{es} .

2.3 Estimation of E_{es} using biomechanical heart model

Model-based E_{es} and time-varying elastance curve estimation The original multiple-beat technique involves first a construction of ESPVR, which is given by linear regression performed on the consecutive End-Systolic Pressure-Volume points obtained in PV loops measured in different loading conditions. Then the slope and the intercept of the ESPVR with the volume axis represent E_{es} and V_0 , respectively. To reproduce this procedure in silico using the calibrated patient-specific model described in Section 2.1, we modified sequentially the afterload by varying Windkessel model parameters. We obtained 5 P-V loops with varying loading conditions and identified the end-systolic pressure-volume point of every P-V loop (corresponding to the aortic valve closing). We performed a linear regression to obtain $E_{\text{es}}^{\text{model}}$ and V_0 , and computed the simulated varying elastance $E^{\text{model}}(t) = P(t)/(V(t) - V_0)$ (see Fig. 1).

Study of the simulated time-varying elastance The simulated and normalised time-varying elastances $E^{N,\text{model}}(t)$ were compared with the $E^N(t)$ obtained experimentally by Suga et al. [16].

3 Results

Table 1 shows the main characteristics of patients and data indicators at baseline obtained from the three patients included in the study.

Table 1. Patients characteristics at baseline. LVEDV: left ventricular end-diastolic volume; SV: stroke volume; P_{ed} : end-diastolic aortic pressure; P_{es} : end-systolic aortic pressure; t_d : pre-ejection time; t_{max} : ejection time.

Patient	Age (<i>yo</i>)	Weight (<i>kg</i>)	Height (<i>cm</i>)	LVEDV (<i>ml</i>)	SV (<i>ml</i>)	P_{ed} (<i>mmHg</i>)	P_{es} (<i>mmHg</i>)	t_d (<i>ms</i>)	t_{max} (<i>ms</i>)
Patient 16	40	58	160	109	71	61	77	107	329
Patient 21	15	58	158	140	91	56	79	84	283
Patient 69	58	88	178	81	45	55	72	77	321

Sensitivity analysis of the existing methods To assess the sensitivity of the Senzaki method, we used the $E^N(t)$ curve from the study of Suga et al. [16]. We generated an interpolation of all the outliers of the curve, to be able to evaluate the effect of the error in measuring E_d^N on the $E_{es}^{senzaki}$ estimation (see Fig. 2, left). We can see in the right panel of Fig. 2 that the standard deviation in estimating E_d^N had a significant impact on the predicted $E_{es}^{senzaki}$. When considering the standard deviation in the $E^N(t)$ data, the value of E_{es} is ranging between half and twice times the predicted value, for all 3 patients.

In order to appreciate the consistency between the method of Senzaki and the method of Chen, we compared the values of E_{es} given by the two methods at baseline and at maximum effect of NOR. The results are presented in Table 2.

Table 2. Results of the end-systolic elastance E_{es} (in mmHg.ml⁻¹) estimation using the method of Senzaki et al. [14], Chen et al. [5], and the biophysical model [2].

Method	Challenge	Patient 16	Patient 21	Patient 69
$E_{es}^{senzaki}$	<i>Baseline</i>	2.88 [1.65 – 4.83]	3.45 [1.85 – 6.76]	6.17 [3.5 – 12.5]
	<i>Noradrenaline</i>	4.68 [2.66 – 8.3]	3.39 [1.86 – 6.17]	7.95 [4.28 – 15.02]
E_{es}^{chen}	<i>Baseline</i>	1.59 [1.23 – 1.94]	1.58 [1.22 – 1.93]	2.51 [2 – 3.08]
	<i>Noradrenaline</i>	2.12 [1.68 – 2.55]	1.83 [1.39 – 2.27]	3.71 [2.83 – 4.57]
E_{es}^{model}	<i>Baseline</i>	2.42	3.35	3.64
	<i>Noradrenaline</i>	5.82	3.05	5.51

Method from biomechanical model For the 3 subjects, we were able to calibrate the biomechanical model and obtain the P-V loop at baseline and after the administration of NOR (see example of calibration in Fig. 3).

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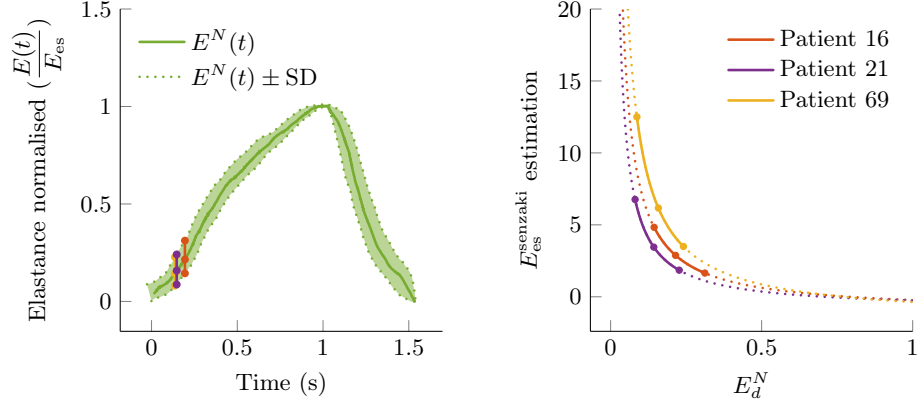


Fig. 2. Normalised elastance curve and effect of the standard deviation (SD) of E_d^N on $E_{es}^{senzaki}$ estimation [14]. Left: Normalised elastance curve (reproduced from Suga et al. [16]) and E_d^N prediction (colored dots) using $\frac{t_d}{t_{max}}$ as obtained by TTE. Right: $E_{es}^{senzaki}$ estimation as function of E_d^N , for the data obtained in the 3 patients. The plain lines represent the $E_{es}^{senzaki}$ for E_d^N inside the ranges given by Suga et al. The dashed line represent the extrapolation of the $E_{es}^{senzaki}$ for E_d^N outside these ranges.

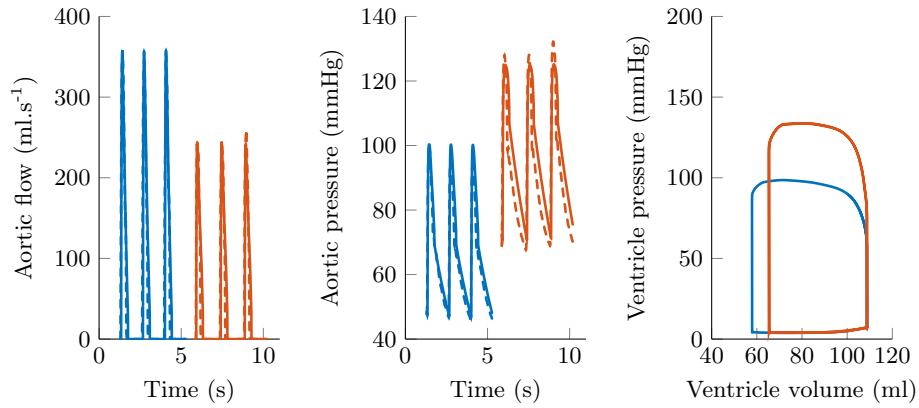


Fig. 3. Example of a calibrated model. The left and the middle panels display respectively the aortic blood flow and pressure at baseline (blue) and at maximal effect of noradrenaline (orange). The simulations (bold) are calibrated using patient's measured data (dashed). The right panel displays pressure-volume loops generated using the results of the aforementioned calibrated simulations at baseline (blue) and at maximal effect of noradrenaline (orange).

Table 2 shows the patient-specific E_{es} prediction from the $E_{es}^{senzaki}$, E_{es}^{chen} and E_{es}^{model} . We can see that E_{es}^{model} is close to $E_{es}^{senzaki}$ for Patients 16 and 21, and located within the ranges given in Suga et al. [16] for all 3 subjects. We can also see that the usage of NOR was associated with an increase of $E_{es}^{senzaki}$ and in E_{es}^{model} except for Patient 21, in whom all methods suggested no change in E_{es} .

Table 3. Sensitivity analysis for E_{es} estimation to relative change in wall thickness, for the Patient 16. The measured wall thickness is in bold.

Wall thickness (% of measured value)	60	80	100	120	150	avg (SD)
E_{es}^{model} (ml.mmHg ⁻¹)	2.56	2.38	2.42	2.73	3.09	2.64 ± 0.29

Out of uncertainties in the estimated E_{es}^{model} , we performed a sensitivity analysis with respect to the error in measuring the input parameters for the model, specifically the error in the wall thickness. The wall thickness was varied by $\pm 50\%$ from the measured value, and the passive and active properties of the model were calibrated accordingly. Table 3 displays the results in E_{es}^{model} estimation for each wall thickness.

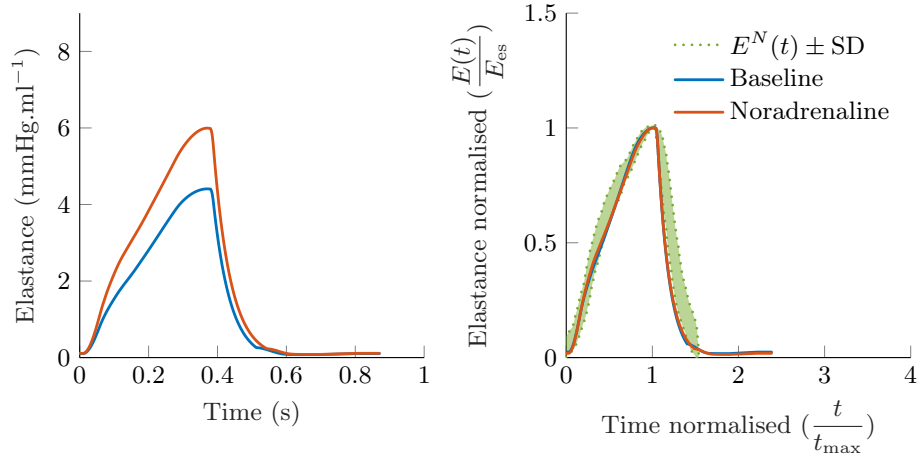


Fig. 4. Example of a patient-specific model-derived time-varying elastance curve. Left: Time-varying elastance at baseline and after NOR administration. Right: Normalised time-varying elastance curve at baseline and after NOR administration, plotted against experimental data (reproduced from [16]).

Fig. 4 demonstrates that the biomechanical model was able not only to estimate E_{es} , but did provide the overall time-varying elastance curve. This example shows that the $E^{model}(t)$ was higher when using noradrenaline (Fig. 4 left panel),

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according to the expected effect of noradrenaline (enhancement of contractility). Furthermore, when $E^{\text{model}}(t)$ curves were normalised as described in Sec. 2.2 (see Fig. 4 right panel), both the time-varying elastance curves (baseline and NOR) were within the physiological ranges described by Suga et al. [16].

4 Discussion

In this paper, we described a mini-invasive multi-beat method to estimate patient-specific time-varying and end-systolic elastance by using biomechanical modelling. As originally described, the E_{es} estimation involves a multiple-beat measurement of P-V loop. For technical concerns, single-beat estimation methods were developed. These methods assume the ESPVR being linear with constant slope of E_{es} , which is extrapolated from the end-diastolic measurement point. However, the slope of the real ESPVR is decreasing when approaching the end-diastolic point [1], deviating the estimated E_{es} . Our method allows to modify loading conditions in order to estimate E_{es} around the measured end-systolic P-V point, where the linearity of ESPVR can be assumed. Furthermore, we demonstrated a very high sensitivity of the single-beat estimation method by Senzaki et al. [14] to E_d^N parameter. Then, we demonstrated a limited accuracy of the method by Chen et al. [5], which introduced some phenomenological terms to the equation (1). Indeed, no concordance with the method of Senzaki et al. [14] could have been observed, the mean values and confidence intervals for $E_{\text{es}}^{\text{chen}}$ estimation falling outside the ranges of $E_{\text{es}}^{\text{senzaki}}$. The reproducibility of the results obtained in the validation studies [5, 14] is therefore questioned. To address these issues, we would have to compare our results against invasive P-V loop measurements, which were not available in our study. Despite the aforementioned limitations, we used the $E_{\text{es}}^{\text{senzaki}}$ estimation as a comparator for an indirect validation of our method. We verified that our simulated $E_{\text{es}}^{\text{model}}$ at least fell within the ranges of the outliers of the $E_{\text{es}}^{\text{senzaki}}$, and that the normalised time-varying elastance $E^{N, \text{model}}(t)$ was consistent with the $E^N(t)$ from Suga et al. [16], in all three subjects even when varying physiology (baseline vs. administration of NOR). We remark in addition that neglecting the standard deviation of the experimentally obtained $E^N(t)$ in the single-beat estimations of E_{es} effectively means decreasing the individuality of the considered subject. We showed, however, that the specificity of patients had a great impact on the E_{es} estimation by these methods. Our framework – based on patient-specific biomechanical modelling – allows a more detailed personalisation. The output of the model is the actual P-V loop and the entire time-varying elastance curve – both being important when considering management of individual patients. Additionally to study the sensitivity of the $E^N(t)$ given by the the range of values in the experiments [16], we could have also explored the sensitivity of the single-beat estimation methods to the accuracy of time measurement. Clearly, during the steepest part of the $E^N(t)$ curve, a small error on the t_d measurement will have a significant impact on the E_d^N , and therefore on the estimation of E_{es} . Finally, the model-derived elastance would be as well a subject of analysis of sensitivity

to the parameters of the model. In this paper, we considered only an example of the uncertainty in ventricular wall thickness, see Table 3. A thorough sensitivity analysis including other input parameters remains to be done in the future.

Our study suffers from several limitations. Indeed, while the Chen's method, allows a non-invasive estimation of E_{es} , our presented framework involves aortic pressure measurement. This preliminary setup will be improved by the methods of transferring the peripheral arterial pressure – practically always available during GA – into the central aortic pressure [6]. Also, the $E^N(t)$ curve was reproduced manually from the study of Suga et al. [16], involving experimental setup from dogs. In the study of Senzaki et al. [14], the authors presented an $E^N(t)$ curve from human data. They showed an absence of variability during the pre-ejection period supporting their final results regarding the reproducibility of their method. This lack of variability is however questioned by Shishido et al. [15]. In a preliminary *in silico* study (data not shown), we also observed a great variability in $E^N(t)$ during the pre-ejection period. For this reason, we did not use the human data made available by Senzaki et al. [14]. We could have compared our method with the method by Shishido et al. [15] aiming at considering the patient's variability of E_d^N estimation, by using a bilinear interpolation of the $E^N(t)$ curve. The comparison with our modelling framework will be explored in the future.

5 Conclusion

By using a patient-specific modelling framework, we proposed a method to estimate E_{es} and the entire time-varying elastance curve, considering individual normalised time-varying elastance variability, at the expense of minimally invasive data measurements. This method provides patient-specific time-varying curve and estimates the value of maximum elastance. Our proposed method could be used both clinically – to assess the patients' heart function – and in cardiac modelling community to provide patient-specific input for simplified models of the heart contraction.

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